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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,844	02/01/2006	Dirk Beher	T1632Y	9399

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EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
02/19/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,844	BEHER ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/29/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims7 is pending and is subject of this office action.

In view of the appeal brief filed on 09/29/2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

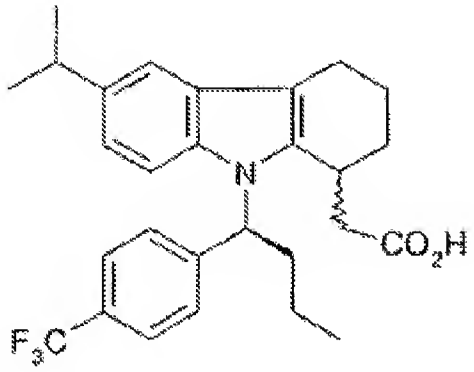
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

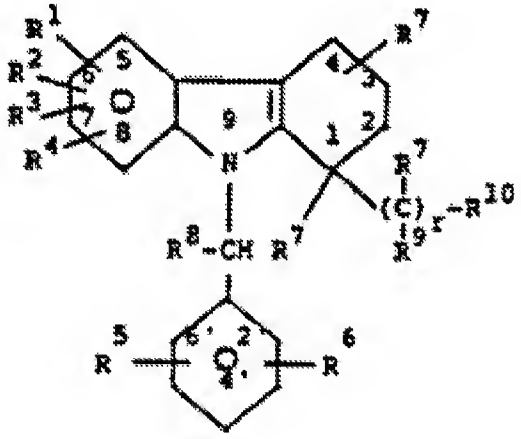
Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ford - Hutchinson (EP 0307077, referenced in instant IDS) in view of Patani et al. (Chemical Reviews, 1996, vol. 96 (8), pages 3147-3176, already of record)

Instant claims are drawn towards the following compound (example 3)

EXAMPLE 13



Ford-Hutchinson teaches compounds of formula (I) shown below (page 4, lines 25-26 and claim 1). Among various substituents taught for each of the R variable below, the following listed substituent read on the instantly claimed compound



I

Wherein R^1= alkyl or alkenyl having 1-6 carbon atoms;

R^2, R^3 and R^4 = H,

R^5 is $(CH)_n M$ where n = 0 and M is CF3 or H

R^6 is - $(CH)_n M$ where n = 0 and M is CF3 or H

R^7 is H

R^8 is H or alkyl of 1-6 carbon atoms

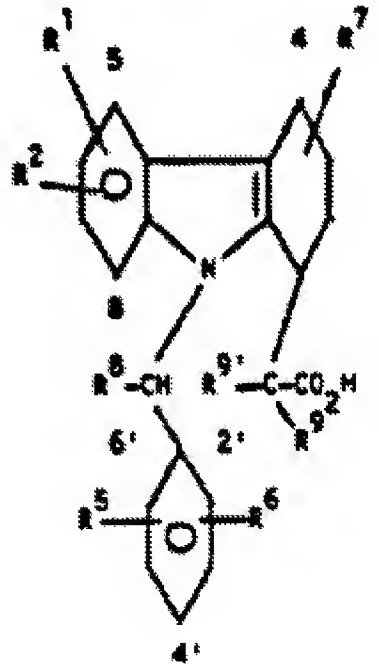
R^9 is H

R^{10} is COOH

Accordingly, the instantly claimed compound is entirely encompassed by the generic compound I taught by Ford- Hutchinson above

Ford-Hutchinson additionally teaches tetahydrocarbazole alkanoic acid compounds of general formula shown below (page 8, line 10-30 and page 10, lines 1 and 11)

Tetrahydrocarbazole
Alkanoic Acids



Compound	R^1	R^2	R^5	R^6	R^9, $R^{9'}$	R^7	R^8
24 (Ex. 24)	6-$CH(Me)_2$	H	4'-Cl	H	H,H	H	H

This compound is structurally similar to the instantly claimed compound except for two substitution differences. The first difference is the substitution at the 4' position on the benzyl ring (R^5 in the above compound of formula 1), wherein Ford-Hutchinson teaches chloride substitution and the instant compounds has CF_3 substitution. The second difference is Ford-Hutchinson's molecule has hydrogen in position R^8 of the compound where as the instantly claimed compound has a propyl group at that position. It is noted that Ford-Hutchinson's generic compound on page 4 teaches the substitution on the position 4' of the benzyl group (R^6 or R^5) to encompass CF_3 (lines 37-38 and 40) and the substitution at R^8 position to include propyl (H or alkyl of 1-6 carbon atoms) group. Apart from the fact that there are only these two differences both of which are actually taught in the generic compound, additional motivation to utilize compound 24 as the lead compound comes from the fact that Ford-Hutchinson not just mentions this compound but in addition teaches the synthetic preparation method for this compound (page 37, lines 29-40) and claims the utility of the compound in reference claim 5, page 54, and line 7).

With regards to the propyl V, hydrogen substitution at position R^8 of compound 24, the number of optional substitution at this position suggested by Ford-Hutchinson' is very limited and includes hydrogen and alkyl group from 1-6 carbon atoms (choice of 7)

as such it would have been obvious to an ordinarily skilled artisan to substitute the hydrogen in compound 24 choosing from these 7 different options, the propyl (3-carbon atoms) option being one of them. In addition Hydrogen and alkyl are deemed obvious variants. In re Henze, 85 USPQ 261 (1950), In re Wood, 199 USPQ 137 (CCPA 1978), and In re Lohr, 137 USPQ 548,549 (CCPA 1963) and the interchange of alkyl and hydrogen is obvious in and of itself, Ex parte Blustone 135, USPQ 199. With regards to appellant's arguments that none of the examples have the propyl substitution at R8 position, "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). In this instance, the number of choices available for substitution at position R8 of Ford-Hutchinson's generic compound is highly limited (7) and encompasses the propyl group. In addition, the substitution of propyl to hydrogen is obvious and as such an ordinarily skilled artisan would be motivated to substitute the hydrogen in compound 24 of Ford-Hutchinson with the propyl group.

With regards to CF_3 substitution at position 4 of the benzyl ring, Ford-Hutchinson's explicitly states this substitutent as possible options for position 4 on the benzyl ring of his compound and teaches 4-CF_3 substitution on the benzyl ring in example of compound 66 of Ford-Hutchinson

Ford-Hutchinson et al. does not teach his compound of formula 24 with a CF_3 substitution at position 4 of the benzyl group instead of chlorine.

However, Patani et al is teaches that the Cl group and CF_3 group are bioisosteres and one can be substituted by the other. It is also noted that chlorine and triflouromethyl compounds are known bioisosteres. Bioisosteres is a strategy of medicinal chemistry for the rational design of new drugs, applied with a lead compound which has a well known chemical structure Patani teaches that halogens have been replaced by electron-withdrawing groups such as a cyano or trifluoromethyl groups and illustrates such a nonclassical replacement of halogen in a structure activity relationship study of cholesystokinin-A (CCK-A) receptor antagonists. CCK –A receptor antagonists have been proposed as potentially useful in the treatment of appetite disorders, abnormalities of gastric motility etc. As illustrated in Table 52 replacement of Cl with nonclassical bioisosteres such as CN or CF_3 resulted in retention of antagonistic activity at the CCK-A receptor (page 3172, section 6, Halogen Bioisosteres). Accordingly, an ordinarily skilled artisan would be motivated to replace the chlorine at position 4 of the benzyl ring in Ford-Hutchinson's compound 24 with CF_3 to obtain a compound with similar properties and utility.

.Accordingly, it would have been *prima facie* obvious to the ordinarily skilled medicinal chemist to synthesize the instantly claimed compounds and compositions. Instantly claimed compound is encompassed by the generic compound taught by Ford-Hutchinson. Ford-Hutchison additionally teaches a compound structurally similar to the instantly claimed compound except for the chloro substitution instead of CF_3 and the H instead of Propyl group at the R8 position. The inventive compounds of Ford-Hutchinson has a large unchanging parent structural nucleus which is identical to

instantly claimed compound and the specific compound 24 taught by Ford-Hutchinson differs from the instantly claimed compound at only two substitution positions both of which can be obviously modified to arrive at the instantly claimed compound as stated above.

Examiner respectfully submits that MPEP 2144.08.II.A.4(c) states, "... consider teachings of a preferred species within the genus. If such a species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. The closer the physical and chemical similarities between the claimed species or subgenus and any exemplary species or subgenus disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner to the genus. See, e.g., Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (and cases cited therein). Cf. Baird, 16 F.3d at 382-83, 29 USPQ2d at 1552

Accordingly one of ordinary skill in medicinal chemistry art would be motivated to make the obvious modifications of the compound 24 taught by Ford-Hutchinson to arrive at the instantly claimed compound. An ordinarily skilled artisan would be imbued with a reasonable expectation of success that compounds and compositions synthesized as taught by Ford-Hutchinson would have utility such as to improve cyclosporine therapy It is to be noted that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and/or similar utilities. “An obviousness rejection based on similarity in chemical structure and/or

function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).

Response to Argument submitted in the Appeal brief dated 09/29/2009

Applicant's arguments with respect to the previous rejection of the claims over submitted in the appeal brief dated 09/29/2009 have been considered but are not persuasive in light of this new ground of rejection set forth here. However, in the interest of a full prosecution history, the Examiner will address Applicant's arguments as they pertain to the present rejection

Appellant traverses the instant rejection under 35 U.S.C 103(a) stating that the fact that a claimed subgenus is encompassed by a prior art genus is insufficient to establish a prima facie case of obviousness and one skilled in the art must be motivated to select the claimed subgenus from the disclosed art genus. Appellant further insists that Ford-Hutchinson teaches a genus with a number of possible substitutions and there is no motivation for one skilled in the art to modify example 24 of Ford-Hutchinson by substituting CF_3 at the 4-position of the benzyl portion of Formula III and a hydrocarbon of 2-10 carbon atoms on the benzylic carbon. Appellant states that none of the examples disclosed by Ford-Hutchinson have a hydrocarbon of 2-10 carbon atoms on the benzylic carbon and as such teach away from the present invention.. Appellants'

further state that obvious to try is not the proper standard to conduct an obviousness determination for chemical compounds.

With respect to appellant's arguments against the primary reference, Ford-Hutchinson, Examiner respectfully submits that Ford-Hutchinson explicitly suggests the instantly claimed compound within a finite list of compounds encompassed by the generic compounds and the exemplified compound. In addition Ford-Hutchinson discloses compound 24 (page 10, line 7). Motivation to utilize compound 24 as the lead compound comes from the fact that Ford-Hutchinson not just mentions this compound but in addition teaches the synthetic preparation method for this compound (page 37, lines 29-40) and claims the utility of the compound in reference claim 5, page 54, line 7). This compound is structurally similar to the instantly claimed compound except for two substitution differences, the substitution of Cl instead of CF3 (instant compound) on the 4' position on the benzyl group, and the substitution of hydrogen in position R8 of the compound instead of a propyl group (instant compound). Substitution of Hydrogen with propyl group is obvious as detailed in the above rejection and with regards to appellant's arguments that none of the examples have the propyl substitution at R8 position, "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including

nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). In this instance, in addition to being obvious, number of choices available for substitution at position R8 of Ford-Hutchinson's generic compound is highly limited (7) and encompasses the propyl group. Appellant's arguments averring "obvious to try" have been considered, but are not found persuasive. "Obvious to try" indicates that there is no reasonable expectation of success provided by the cited prior art. However, in the instant case, it is reasonably expected that a substitution of propyl to hydrogen and CF3 to chlorine in the reference compound 24 would result in compounds which would potentially have the same utility as the parent compounds since hydrogen and propyl are obvious variants and Cl and CF_3 are bioisosteres, absent evidence to the contrary. No such evidence is seen to be present herein.

With respect to Patani et al. references appellants argue that Patani et al. teaches substitution on entirely different core molecules for different biological targets and would not be utilized by the ordinarily skilled artisan in designing compounds that limit cyclosporine induced nephrotoxicity or modulate the action of gamma secretase. Appellants further states that Patani demonstrates unpredictability in the chemical arts as substitution of CF_3 for Cl resulted in less potent analogues for the demonstrated UrdPase inhibitors but retention of activity for the CCK-A receptor antagonists. Examiner respectfully submits that Patani et al. is used in this rejection as an evidentiary document to demonstrate the bioisosterism between chlorine and triflouromethyl group and that it is one of the common exchanges made during drug

development to determine the structure activity relationship of the lead compound. Patani is not used here for their teachings of any of the chemical compounds recited within. While agreeing with the appellants that Patani et al demonstrated varying results with different compounds with the substitution of CF_3 for Chlorine, examiner respectfully submits that Patani does not teach away from this substitution, the fact that there is a change in the activity which can be positive is evidence that this non-classic substitution of CF3 to Cl would be a potential tool in drug development. It is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Accordingly, Claim 7 is appropriately rejected as being obvious over the teachings of Ford-Hutchinson in view of Patani et al.

Conclusion

Claim 7 is rejected. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614